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     FILE 'HCAPLUS' ENTERED AT 08:11:09 ON 22 JUL 2008
L1         43846 S MORPHINE
L2         13888 S HYDROBROMIDE
L3        948385 S STABILITY OR (SHELF LIFE) OR DECOMPOSITION
L4            14 S L1 AND L2 AND L3
L5           530 S L2 AND L3
L6            12 S L4 AND (PY<2003 OR AY<2003 OR PRY<2003)
L7           357 S L5 AND (PY<2003 OR AY<2003 OR PRY<2003)

     FILE 'STNGUIDE' ENTERED AT 08:11:21 ON 22 JUL 2008

     FILE 'HCAPLUS' ENTERED AT 08:11:28 ON 22 JUL 2008

     FILE 'STNGUIDE' ENTERED AT 08:11:29 ON 22 JUL 2008

     FILE 'REGISTRY' ENTERED AT 08:33:00 ON 22 JUL 2008
                EXP MORPHINE-6-GLUCURONIDE/CN
                EXP 6-GLUCURONOMORPHINE/CN
                EXP MORPHINE/CN
                EXP MORPHINE 6-GLUC/CN
L8            36 S E4-#5
L9             2 S E4-E5

     FILE 'HCAPLUS' ENTERED AT 08:34:43 ON 22 JUL 2008
L10          612 S L9
L11       307371 S BROMIDE OR HYDROBROMIDE
L12           21 S L10 AND L11
L13           11 S L12 AND (PY<2003 OR AY<2003 OR PRY<2003)
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=> file hcaplus
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                         ENTRY    SESSION
FULL ESTIMATED COST                                       0.84       0.84

FILE 'HCAPLUS' ENTERED AT 08:11:09 ON 22 JUL 2008
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PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
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FILE COVERS 1907 - 22 Jul 2008  VOL 149 ISS 4
FILE LAST UPDATED: 20 Jul 2008  (20080720/ED)

HCAplus now includes complete International Patent Classification (IPC)
reclassification data for the second quarter of 2008.

New CAS Information Use Policies, enter HELP USAGETERMS for details.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

=> s morphine

L1       43846 MORPHINE

=> s hydrobromide

L2       13888 HYDROBROMIDE

=> s stability or (shelf life) or decomposition

        753637 STABILITY
         31193 SHELF
        351213 LIFE
         17393 SHELF LIFE
                 (SHELF(W)LIFE)
        193599 DECOMPOSITION
L3      948385 STABILITY OR (SHELF LIFE) OR DECOMPOSITION

=> s l1 and l2 and l3

L4          14 L1 AND L2 AND L3

=> s l2 and l3

L5         530 L2 AND L3

=> s l4 and (PY<2003 or AY<2003 or PRY<2003)

      22935598 PY<2003
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       4491924 AY<2003
       3960009 PRY<2003
L6          12 L4 AND (PY<2003 OR AY<2003 OR PRY<2003)

=> s l5 and (PY<2003 or AY<2003 or PRY<2003)

      22935598 PY<2003
       4491924 AY<2003
       3960009 PRY<2003
L7         357 L5 AND (PY<2003 OR AY<2003 OR PRY<2003)

=> file stnguide

COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                         ENTRY    SESSION
FULL ESTIMATED COST                                       2.69       3.53

FILE 'STNGUIDE' ENTERED AT 08:11:21 ON 22 JUL 2008
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FILE CONTAINS CURRENT INFORMATION.
LAST RELOADED: Jul 18, 2008 (20080718/UP).

=> d l6 1-12 ti abs bib
YOU HAVE REQUESTED DATA FROM FILE 'HCAPLUS' - CONTINUE? (Y)/N:y



L6   ANSWER 1 OF 12  HCAPLUS  COPYRIGHT 2008 ACS on STN
TI   Morphine-6-glucuronide salts and stability thereof
AB   Several salts of morphine-6-glucuronide are prepared, and the
     hydrobromide salt (M6G.HBr) is surprisingly stable compared to
     other M6G salts and M6G free base.  Use of M6G.HBr as a medicament, in
     particular as an analgesic, and methods of making M6G.HBr are described.
AN   2004:162705  HCAPLUS <<LOGINID::20080722>>
DN   140:205122
TI   Morphine-6-glucuronide salts and stability thereof
IN   Graham, John Aitken
PA   Cenes Limited, UK
SO   PCT Int. Appl., 27 pp.
     CODEN: PIXXD2
DT   Patent
LA   English
FAN.CNT 1
     PATENT NO.          KIND   DATE        APPLICATION NO.         DATE
     ---------------     ----   --------    --------------------    --------
PI   WO 2004016633        A1    20040226    WO 2003-GB3562          20030814 <--
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
             CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
             GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
             LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM,
             PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN,
             TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
         RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
             KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES,
             FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR,
             BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
     CA 2494812           A1    20040226    CA 2003-2494812         20030814 <--
     AU 2003255790        A1    20040303    AU 2003-255790          20030814 <--
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     EP 1537132           A1    20050608    EP 2003-787894         20030814 <--
     EP 1537132           B1    20060104
         R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
             IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK
     JP 2006500360        T     20060105    JP 2004-528672         20030814 <--
     AT 315041            T     20060215    AT 2003-787894         20030814 <--
     ES 2256790           T3    20060716    ES 2003-787894         20030814 <--
     ZA 2005001053        A     20050829    ZA 2005-1053           20050204 <--
     IN 2005CN00181       A     20070907    IN 2005-CN181          20050214 <--
     NO 2005001261        A     20050311    NO 2005-1261           20050311 <--
     US 20060166900       A1    20060727    US 2005-524149         20050628 <--
PRAI GB 2002-18811        A     20020814  <--
     WO 2003-GB3562       W     20030814
RE.CNT  3     THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD
              ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6   ANSWER 2 OF 12  HCAPLUS  COPYRIGHT 2008 ACS on STN
TI   Fosinopril formulation
AB   A pharmaceutical formulation is provided comprising fosinopril which is
     the prodrug of an angiotensin converting enzyme (ACE) inhibitor,
     fosinoprilat.  The formulation is characterized by comprising in the range
     of about 0.25 to about 5 % glyceryl dibehenate which has been found to be
     a highly useful lubricant in the manufacture of tablets according to the
     present invention, enhancing the stability of fosinopril as
     compared to prior art formulations.  For example, tablets were formulated
     containing fosinopril Na 5, lactose monohydrate 59, starch 12, croscarmellose
     sodium 2, microcryst. cellulose 20, and glyceryl dibehenate 2 mg/each.
AN   2003:757534  HCAPLUS <<LOGINID::20080722>>
DN   139:265788
TI   Fosinopril formulation
IN   Eyjolfsson, Reynir
PA   Delta Hf., Iceland
SO   PCT Int. Appl., 9 pp.
     CODEN: PIXXD2
DT   Patent
LA   English
FAN.CNT 1
     PATENT NO.           KIND   DATE        APPLICATION NO.        DATE
     ---------------      ----   --------    --------------------   --------
PI   WO 2003077929         A1    20030925    WO 2003-IS13           20030319 <--
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
             CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
             GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
             LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM,
             PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT,
             TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
         RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
             KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES,
             FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR,
             BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
     AU 2003208599         A1    20030929    AU 2003-208599         20030319 <--
     EP 1531831            A1    20050525    EP 2003-706893         20030319 <--
     EP 1531831            B1    20051228
         R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
             IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK
     AT 314076             T     20060115    AT 2003-706893         20030319 <--
     PT 1531831            T     20060531    PT 2003-706893         20030319 <--
     ES 2256721            T3    20060716    ES 2003-706893         20030319 <--
     US 20050256086        A1    20051117    US 2004-507918         20040916 <--
     US 7045511            B2    20060516
     NO 2004004390         A     20041215    NO 2004-4390           20041018 <--
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PRAI IS 2002-6315 A 20020319 <--
WO 2003-IS13 W 20030319
RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 3 OF 12 HCAPLUS COPYRIGHT 2008 ACS on STN
TI Preparation of aqueous clear solution dosage forms with bile acids
AB Compns. for pharmaceutical and other uses comprise clear aqueous solns. of bile acids which do not form any detectable ppts. over selected ranges of pH values of the aqueous solution The compns. comprise (i) water, (ii) a bile acid component in the form of a bile acid, bile acid salt, or a bile acid conjugated with an amine by an amide linkage; and (iii) either or both an aqueous soluble starch conversion product and an aqueous soluble non-starch polysaccharide. The composition remains in solution without forming a precipitate over a range of pH values and, according to one embodiment, remains in solution for all pH values obtainable in an aqueous system. The composition may further contain a pharmaceutical compound, such as insulin, heparin, bismuth compds., amantadine and rimantadine. For example, solution dosage forms that did not show any precipitation at any pH were prepared containing ursodeoxycholic acid (UDCA) 22 g, 1N NaOH 75 mL, chenodeoxycholic acid (CDCA) 3 g, maltodextrin 875 g, bismuth citrate 4 g, citric acid or lactic acid as needed, and purified water to make 1 L.
AN 2002:185616 HCAPLUS <<LOGINID::20080722>>
DN 136:252482
TI Preparation of aqueous clear solution dosage forms with bile acids
IN Yoo, Seo Hong
PA USA
SO U.S. Pat. Appl. Publ., 35 pp., Cont.-in-part of U. S. 6,251,428.
CODEN: USXXCO
DT Patent
LA English
FAN.CNT 5

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 20020031558	A1	20020314	US 2001-778154	20010205 <--
	US 7303768	B2	20071204		
	US 6251428	B1	20010626	US 1999-357549	19990720 <--
	US 20030186933	A1	20031002	US 2002-309603	20021204 <--
	US 7166299	B2	20070123		
	US 20050158408	A1	20050721	US 2004-996945	20041124 <--
	AU 2004325203	A1	20060601	AU 2004-325203	20041124
	CA 2588168	A1	20060601	CA 2004-2588168	20041124
	EP 1819318	A1	20070822	EP 2004-812094	20041124
	R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR				
	CN 101065110	A	20071031	CN 2004-80044467	20041124
	BR 2004019213	A	20071218	BR 2004-19213	20041124
	JP 2008521800	T	20080626	JP 2007-543006	20041124
	AU 2006203315	A1	20060824	AU 2006-203315	20060803 <--
	US 20070072828	A1	20070329	US 2006-522162	20060915 <--
	IN 2007CN02532	A	20070907	IN 2007-CN2532	20070612
	KR 2007098821	A	20071005	KR 2007-714361	20070622
	US 20080057133	A1	20080306	US 2007-934505	20071102 <--
PRAI	US 1998-94069P	P	19980724 <--		
	US 1999-357549	A2	19990720 <--		
	US 2000-180268P	P	20000204 <--		
	AU 2001-36685	A3	20010205 <--		
	US 2001-778154	A3	20010205 <--		

US 2004-996945 A2 20041124
WO 2004-US39507 A 20041124
RE.CNT 211 THERE ARE 211 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 4 OF 12 HCAPLUS COPYRIGHT 2008 ACS on STN
TI The effect of time of storage on quality of injection solutions in ampuls
AB The stability of 16 types of solns. for injection was investigated. The solns. were stored for 10 years at 10-12° or 18-20°, for 15 days at 45°, and for 3 days at -55°. Injection solns. of atropine sulfate, glucose, MgSO4, strychnine nitrate, scopolamine-HBr, NaCl, and CaCl2 are stable for 10 years. The time of storage can be substantially prolonged in the case of ascorbic acid, Na3AsO4, thiamine-HCl, morphine-HCl, Novocaine, omnopone, Na2S2O3, ephedrine-HCl, and a mixture of caffeine with NaOBz if solns. are kept at 10-12°.
AN 1964:22719 HCAPLUS <<LOGINID::20080722>>
DN 60:22719
OREF 60:3955a-b
TI The effect of time of storage on quality of injection solutions in ampuls
AU Vaisman, G. A.; Yashchenko, D. V.
CS Inst. Advanced Med. Training, Kiev
SO Farmatsevtichnii Zhurnal (Kiev) (1963), 18(2), 33-7
CODEN: FRZKAP; ISSN: 0367-3057
DT Journal
LA Unavailable

L6 ANSWER 5 OF 12 HCAPLUS COPYRIGHT 2008 ACS on STN
TI Closure of the oxide bridge in the morphine series
GI For diagram(s), see printed CA Issue.
AB cis-Dihydrothebainone (I, R = H) was brominated in glacial AcOH to give I (R = Br).HBr, (II), m. 215-25° (decomposition), λ 5.79, [α]25D -45°. Warming II in H2O gave III.HBr, [α]23D -89° (c 1.21, H2O). Treatment of 200 mg. II in 5 cc. H2O and 2 cc. AcOH with 13 ml. 7N NaOH gave 81% III, m. 204-6.5° (EtOAc), λ 5.79 μ. II (200 mg.) in 10 ml. AcOH was treated with 84 mg. 2,4-dinitrophenylhydrazine (DNP) to give 86 mg. (IV) [R = 2,4-(O2N)2C6H3NHN] (IVa), m. 201-4°. IIa (200 mg.) was dissolved in 8 ml. Me2SO and the solution was diluted with 100 ml. H2O after 2 hrs., and extracted with Et2O to give 31 mg. (-)-1-bromosinomeninone (V), m. 224° (decomposition); methiodide m. 244-6°. trans-Dihydrothebainone (VI) perchlorate (4.07 g.) was suspended in 10 ml. dilute NH4OH, and VI was extracted with CHCl3, and brominated in glacial AcOH to give 74% trans-1,7-dibromodihydrothebainone hydrobromide (VII), m. 205-6° (decomposition), [α]27D 11°, λ 5.80 μ. Treatment of crude VII with NaOH gave 13% trans-1-bromodihydrocodeinone (VIII) which was insol. in aqueous NaOH. The basic aqueous solution was acidified with AcOH and extracted with CHCl3 to give cis-1-bromothebainone, IV (R = O), m. 193-5° (EtOAc), λ 6.01 μ; 2,4-dinitrophenylhydrazone, m. 205°. VIII was also prepared from VI by bromination in AcOH and dehydrobromination in boiling collidine, m. 165-6°, λ 5.79 μ [α]25D, -65°. VII (200 mg.) in 5 ml. MeOH was added to 85 mg. MeONa in 15 ml. MeOH, and the solution was concentrated to dryness after 6 hrs. to give 38 mg. VIII, which was reduced by Zn dust-NH4Cl in EtOH to give trans-1-bromodihydrothebainone, (IX), m. 170-2°; HClO4 salt m. 272-4° (decomposition), [α]26D -17.5°. VIII (286 mg.) was refluxed with 1 ml. D2O and 0.1 g. K2CO3 in 10 ml. dioxane 6 hrs., and D analysis indicated 2 exchangeable H atoms. III behaved similarly. VII

(200 mg.) in 10 ml. AcOH was treated with 85 mg. DNP, and the mixture was heated on a steam bath 30 min. to give 153 mg. IVa, m. 202-5°. Tribromination of 0.961 g. I in 15 ml. AcOH at 10° gave 1.45 g. cis-1,7,dibromodihydrocodeinone hydrobromide (X), m. 195 (decomposition), (95% EtOH), λ 5.74 μ, [α]27D -184°, which was also prepared by bromination of cis-dihydrocodeinone (XI). X (300 mg.) in 15 ml. MeOH was treated with 0.06 g. NaBH4 in 10 ml. MeOH, the solution evaporated to dryness after 12 hrs., and the residue refluxed with Zn dust in AcOH to give 90 mg. 1-bromodeoxycodeine C, (XII), m. 179-81°, λ, 6.02 μ. Sublimution yielded anhyds. material, m. 210°. The reaction of 200 mg. X with 25 ml. 4N KOH at 40° gave 113 mg. V, m. 224° (decomposition). X (200 mg.) in 10 ml. AcOH was heated with 84 mg. DNP to yield 68 mg. cis-1-bromocodeinone 2,4-dinitrophenylhydrazone, m. 221-4° (EtOAc). X (200 mg.) was allowed to stand 25 hrs. with 15 ml. Me2SO at room temperature to give 43 mg. (-)-1-bromosinomeneine ketone, m. 196-7°. VIII was the first trans-pentacylic compound of the morphine series to be prepared, and was of normal stability. The differences in the cyclization ease of the trans and cis compds. were discussed.

AN 1963:46910 HCAPLUS <<LOGINID::20080722>>
DN 58:46910
OREF 58:7988a-g
TI Closure of the oxide bridge in the morphine series
AU Gates, Marshall; Shepard, Marvin S.
CS Univ. of Rochester, Rochester, NY
SO Journal of the American Chemical Society (1962), 84, 4125-30
CODEN: JACSAT; ISSN: 0002-7863
DT Journal
LA Unavailable

L6 ANSWER 6 OF 12 HCAPLUS COPYRIGHT 2008 ACS on STN
TI Testing of medicinal solutions in ampuls for decomposition products formed by sterilization
AB Various medicinals (mostly alkaloids) were filled into ampuls and sterilized at 120° for 8 min., then compared with nonsterilized products by paper chromatography and colorimetric methods for decomposition products. Heat sterilization was recommended (in preference to tyndallization) for: atropine salts, strychnine, adrenaline salts (with addition of Na2S2O5 and chloretone), ephedrine-HCl, thiamine-HCl, nicotinic acid, glycerol, iodine solution, AgNO3. Bacteria-excluding filtration was recommended for: hyoscyamine-HBr and -HCl, scopolamine-HBr (I), morphine-HCl (II) (also with atropine sulfate (III)), papaverine, adrenaline-HCl (in case prepared only with Na2S2O3), and CaBr2. For prepns. which show a yellow coloration (I, II, III), a pharmacol. test is needed to determine potency.

AN 1959:36552 HCAPLUS <<LOGINID::20080722>>
DN 53:36552
OREF 53:6533a-c
TI Testing of medicinal solutions in ampuls for decomposition products formed by sterilization
AU Kitzing, W.
CS VEB Arzneimittelwerk, Dresden, Germany
SO Pharmazie (1958), 13, 530-4
CODEN: PHARAT; ISSN: 0031-7144
DT Journal
LA Unavailable

L6 ANSWER 7 OF 12 HCAPLUS COPYRIGHT 2008 ACS on STN
TI The phenyldihydrothebaines
AB cf. C.A. 33, 3380.5. The peculiar behavior of phenyldihydrothebaine (I) (cf. loc. cit.) indicates that it must be a mixture of isomers. This point

is now investigated. To 330 cc. 2 M PhMgBr in 200 cc. boiling C6H6 100 g. thebaine in 1900 cc. C6H6 is added over a period of 2 h. with stirring. After addnl. refluxing for 6 h. the mixture is decomposed with saturated NH4Cl, extracted with C6H6, and the combined C6H6 exts. extracted with 2 N HCl. The base is liberated from the acid solution with NH4OH, extracted with ether in the presence of a little Na2S2O4, and evaporated, leaving a purple sirup. This is taken up in 150 cc. absolute EtOH and treated with 55 g. 60% HClO4 in 120 g. ice-cold absolute EtOH, giving a mixture of perchlorates (II). From 8 such runs 1102 g. II (89%) is obtained. II is converted into the HCl salts in alc. solution, from which, after 12 h. standing at 0°, 75-8% (+)-αphenyldihydrothebaine-HCl (IIIa) crystallizes. The final mother liquor contains the (+)-δ-phenyldihydrothebaine (IV). The free base (III) of IIIa is a glasslike solid but crystallizes with 1 mol. EtOH in prisms, m. 40-70°, [α]D20 10.2° (c 1.98, EtOH). III, b0.1 150°, [α]D20 25.3° (c 0.75, EtOH), necessarily contains some (-)-δ-phenyldihydrothebaine (V). III is soluble in alkali and is precipitated with CO2 or NH4Cl, gives no color reaction with FeCl3 but an intense red color with diazosulfanilic acid (VI). III is not catalytically hydrogenated in neutral solution III HClO4 salt (IIIb) m. 248° (in vacuo, decomposition), [α]D26 35° (c 0.21, EtOH), [α]D20 8.2° (c 0.98, Me2CO); methiodide (IIIc) m. 216.5-18°, [α]D26 42.7° (c 0.36, EtOH). Boiling vigorously 307 g. IIIc in 11.30% KOH 5 min. gives a glassy solid which is shaken with H2O and ether. Keeping the ether solution at 0° gives 52.8% (+)-α-phenyldihydrothebaineisomethine (VII). The mother liquor is evaporated to a sirup, dissolved in 150 cc. EtOH, and 270 cc. EtOH and 10% aqueous HClO4 (1:1) are added, causing the separation of 14% unchanged impure IIIb, m. 223-30°, [α]D 4°, which is immediately filtered off. From the filtrate 3% III normal methine (VIII) HClO4 (VIIIa), m. 93-122°, [α]D -34°, soon crystallizes. On cooling the mother liquor at 0° 19% more VII.HClO4 (VIIa), m. 105-15°, [α]D -127°, seps. VII is purified via VIIa, crystallizing with 1 EtOH, clusters of needles, m. 111-17° (gas evolution), [α]D25 -197° (c 0.58, EtOH, 1.21, AcOEt); VII b0.1 120°, m. 101°, [α]D20 -280° (c 2.73, EtOH); methiodide (VIIb), felted needles, crystallizing with 2 H2O, m. 100-10°, [α]D25 -207° (c 1.62, EtOH), m. 159-60° (H2O free). VII gives a neg. test with FeCl3 and a red color with VI. When VII is boiled 1 min. with concentrated HCl, (+)-α-phenyl-9-dimethylamino-6-methoxythebenediene (IX) is formed as an oil which is insol. in alkali and gives a neg. test with VI; HClO4 salt m. 168°, [α]D22 26.5° (c 0.11, EtOH); methiodide (IXa), long square-ended prisms, m. 212-13°, [α]D20 0.6° (c 1.58, EtOH). Degradation of IXa by boiling with 6% NaOEt 3 min. gives dl-phenyl-6-methoxythebenetriene (X), crystals from AcOEt, m. 162.5-3°, [α]D20 0.0° (c 0.48, Me2CO). X is indifferent to acetylation, gives a neg. test with PhN2Cl and a blue-violet fluorescence in AcOEt. Hydrogenation of X in AcOEt in the presence of PtO2 gives dl-phenyl-6-methoxythebenediene (XI), lustrous leaflets, m. 119-20.5°, [α]D20 0.0° (c 0.32, AcOEt). Hydrogenation of X in AcOEt in the presence of a little AcOH gives dl-phenyl-6-methoxythebenane, long prisms, m. 80-3.5°, [α]D20 0.0° (c 0.37, AcOEt). When VIIb is refluxed 1 h. with 6% EtONa 78% (+)-vinylphenyldihydrothebaol (XII), m. 149°, [α]D25 47.1° (c 0.51, AcOEt), is obtained and gives an orange-red dye with diazotized PhNH2. With 30% KOH the yield of XII drops to 33% with partial racemization, [α]D20 21.4°. Acetylation of XII with Ac2O in C5H5N 50 h. gives (+)-acetylvinylphenyldihydrothebaol, square plates, m.

145.5-7°, [α]D23 24.7° (c 0.32, AcOEt). Hydrogenation of XII in neutral AcOEt in the presence of PtO2 gives (+)-ethylphenyldihydrothebaol (XIII), m. 118°, [α]D25 -74.4° (c 0.31, AcOEt), which is identical with XIII obtained from XVIb. Ac derivative (XIIIa), rectangular plates, m. 82.5-3°, [α]D25 -77.0° (c 0.31, AcOEt). When the hydrogenation is carried out in the presence of a little AcOH 36 h. (+)-ethylphenylhexahydrothebaol is obtained as an oil; Ac derivative (XIV), crystals from 70% EtOH, m. 82.5-3°, [α]D20 -23.4° (c 0.26, AcOEt). Cyclization of XII by boiling it 10 min. with concentrated HCl-dioxane (10:1) gives a phenolic resin (XV), [α]D20 -115° (c 1.09, Me2CO) after distillation in a high vacuum. XV is methylated with Me2SO4 and NaOH, giving a nonphenolic resin with [α]D20 -111° (c 0.48, Me2CO). It is racemized by boiling 10 min. with EtONa, giving X, m. 161-3°, [α]D26 0.0° (c 0.96, Me2CO). Hydrogenation of 11.5 g. VII in 300 cc. EtOH with 50 mg. PtO2 30 min. and addition of 75 cc. 60% HClO4 until the fluorescence disappears give 13.2 g. (+)-α-phenyldihydrothebainedihydroisomethine-HClO4, needles, crystallizing with 2 H2O, m. 85-7°, m. 111-17° (H2O-free), [α]D25 -104° (c 1.08, EtOH); free base, liberated with NH4OH, m. 70-2°, [α]D20 -175° (c 1.06, EtOH); methiodide (XVIb), crystallizing with 1.5H2O, m. 212-13°, [α]D25 -121° (c 2.86, EtOH). Degradation of XVIb by boiling with 6% NaOEt 1.5 h. gives XIII, m. 118°, [α]D20 -76.7° (c 0.36, AcOEt); Ac derivative, prepared with Ac2O in C5H5N, rectangular plates, m. 122.5-3°, [α]D20 -77.8° (c 0.32, AcOEt), is identical with XIIIa. Hydrogenation of 3 g. VII in 50 cc. EtOH and 50 cc. N HCl with 400 mg. PtO2 and liberating the base with NH4OH after removal of the EtOH give (+)-α-hexahydrophenyldihydrothebainedihydroisomethine, long needles, m. 108-8.5°, [α]D20 -24.2° (c 1.78, EtOH), which shows a brilliant yellow-green fluorescence in alc.; methiodide m. 207-8°, [α]D20 -14.7° (c 1.16, EtOH), and is isomeric with IXa and XXVIIa. VIIIa, purified by repeated crystallization, m. 106-20° (decomposition), [α]D20 -60.3° (c 0.26, EtOH) [α]D20 -34° (c 1.12, Me2CO); VIII m. 126-7°, [α]D20 -46.5° (c 0.86, EtOH); methiodide (VIIIb) m. 244° (evacuated tube), [α]D20 -51.5° (c 0.41, EtOH). VIII is soluble in dilute NaOH, gives a red dye with VI, and is not affected by boiling HCl. VIII is very resistant to degradation and on boiling VIIIb with 40% KOH it gives the methohydroxide, long felted yellow needles, which when distilled in vacuo at 160° gives dl-vinylphenyldihydrothebaol (XVII), m. 149.5°, [α]D20 0.0° (c 0.39, AcOEt). Evaporation of the alc. mother liquor of IIIa in vacuo leaves a sirup from which 7.8% IV, needles, m. 143.5°, [α]D20 -110° (c 1.10, CHCl3), [α]D20 -131° (c 0.87, MeCO), is isolated; HClO4 salt (IVa) m. 209-13°, [α]D24 -44.5° (c 1.23, EtOH); methiodide (IVb), crystallizing with 1 MeOH, m. 206-8°, [α]D23 -43° (c 0.72, EtOH). Degradation of IVb by boiling it 15 min. with 30% KOH and decomposing the K salt with NH4Cl gives 70% (+)-δ-phenyldihydrothebaineisomethine (XVIII), long prisms, m. 117-19°, [α]D25 153° (c 0.63, EtOH); it sublimes at 140°/0.1 mm. in long feathery crystals (HClO4 salt, crystallizing with 2 EtOH, m. 114-16°, [α]D23 89.6° (c 0.67, EtOH); methiodide (XVIIIb), m. 202-3°, [α]D24 108° (c 0.99, EtOH)). Boiling XVIIIb with EtONa gives XII, m. 149°, [α]D24 46.6° (c 0.58, AcOEt). Reduction of XVIII in dilute AcOH with PtO2 gives an oily (+)-δ-phenyldihydrothebainedihydroisomethine (methiodide m. 217-19° (decomposition), [α]D25 145° (c 0.32, EtOH), which on further degradation with EtONa gives 50% XIII, m. 118°, [α]D25 -76.0° (c 0.27, AcOEt)). Cyclization by boiling XVIII 5 min. with concentrated HCl, liberation of the base with NaOH, and treating it with MeI

give (+)-δphenyl-9-dimethylamino-6-methoxythebenediene methiodide, m. 170-3°, [α]D26 -3.8° (c 1.05, EtOH). Boiling the latter with EtONa gives X, m. 161-2°, [α]D25 0.0° (c 0.38, Me2CO). III (168 g.) is heated in an evacuated tube 80 h. at 200°, the yellow fluorescent resin dissolved in 250 cc. EtOH, seeded with a sample of V, and kept 2 days at 3°, causing the crystallization of 16% V, needles, m. 143.5°, [α]D20 110° (c 1.10, U.S.P. CHCl3), [α]D20 131° (c 0.66, Me2CO). V is soluble in alkali, gives no FeCl3 test but a brilliant red color with VI. V is not hydrogenated in neutral solution From the alc. mother liquor 70% unchanged IIIb is recovered. HClO4 salt of V m. 209-13°, [α]D24 42.8° (c 0.63, EtOH); methiodide (Vb) crystallizes with 1 MeOH and m. 206-8°, [α]D20 44° (c 0.32, EtOH). Boiling Vb 5 min. with 30% KOH gives 98% (-)-δ-phenyldihydrothebaineisomethine (XIX), long leaflets, m. 117-19°, [α]D20 -154° (c 0.92, EtOH); it sublimes at 140°/0.1 mm. in long feathery crystals (HClO4 salt m. 114-16°, [α]D20 -90° (c 0.69, EtOH); methiodide (XIXb) m. 202-3°, [α]D25 -105° (c 0.40, EtOH)). Degradation of XIXb with EtONa gives (-)-vinylphenyldihydrothebaol (XX), m. 149.5-50°, [α]D22 -47.4° (c 0.17, AcOEt). XX when mixed with an equal part of XII gives a product, m. 146-7°, [α]D20 0.0° (c 0.21, AcOEt), which is probably identical with XVII. When 3 g. III is heated 60 h. under a high vacuum at 200° a dark glass is formed from which on crystallization from EtOH 59% III is isolated as IIIb, large glassy crystals, m. 248° (evacuated tube, decomposition), [α]D20 37° (c 0.209, EtOH). When 7.6 g. IV is heated in an evacuated tube 50 h. at 200°, 23% unchanged IV is recovered. From the alc. mother liquor 74% (-)-α-phenyldihydrothebaine (XXI) is isolated as the HClO4 salt (XXIa), m. 248° (evacuated tube, decomposition), [α]D20 -8.0° (c 1.25, Me2CO), [α]D20 -35° (c 0.20, EtOH). XXI is a glass, [α]D20 -10° (c 0.22, EtOH); methiodide (XXIb) m. 216°, [α]D20 -43.6° (c 0.27, EtOH). Degradation of XXIb by boiling 5 min. with 30% KOH gives 95% (-)-α-phenyldihydrothebaineisomethine (XXII), isolated as the HClO4 salt, m. 111-16°, [α]D20 197° (c 0.61, EtOH), crystallizing with 1 EtOH; XXII m .101°, [α]D20 281° (c 1.12, EtOH). Hydrogenation of 30 g. III with PdCl2 and gum arabic 20 min. gives 85% (+)-phenyltetrahydrothebaimine (XXIII), pentagonal plates, m. 120-1°, [α]D20 -35° (c 1.14, Me2CO), [α]D20 -4.2° (c 1.19, 10% AcOH). XXIII is soluble in alkali, gives no FeCl3 test but a red dye with VI. Reduction of IV in the same way but for 18 h. also gives XXIII, m. 121°, [α]D20 -32.7° (c 2.63, Me2CO). Warming XXIII in C6H6 with MeI gives 46% (+)-phenyltetrahydrothebaimine N-methomethiodide (XXIIIa). It is dimorphous; it m. 235° (evacuated tube), and, after gentle grinding, 250-3°, [α]D24 -5.2° (c 2.67, MeOH), [α]D25 -3.3° (c 2.11, EtOH). XXIIIa, [α]D25 -5.8° (c 1.21, MeOH), [α]D25 -3.5° (c 1.73, EtOH), is also obtained from IV. Hydrogenation of VIII in EtOH with PtO2 gives XXIII which is converted into 100% methiodide, [α]D25 -5.4° (c 3.30, MeOH), -3.9° (c 2.85, EtOH), identical with XXIIIa. Hydrogenation of 5 g. V 4 h. in the same way as IV gives (-)-phenyltetrahydrothebaimine (XXIV), pentagonal plates, m. 121°, [α]D20 35.5° (c 1.01, Me2CO), subliming as clusters of needles at 150° in a high vacuum. N-methomethiodide m. 235° (evacuated tube), [α]D20 5.3° (c 2.31, MeOH). Reduction of XXI in dilute AcOH 2.5 h. gives 94% XXIV, m. 120.5-1°, [α]D20 35.5° (c 1.0, Me2CO), [α]D20 4.9° (c 1.02, 10% AcOH). Crystallization of equal parts of XXIII and XXIV gives dl-phenyltetrahydrothebaimine (XXV), bundles of long

crystals, m. 134°, [α]D20 0.0° (c 0.6, Me2CO). The imines from the IV, XXI, from the IV, V, and from the III, XXI series, when crystallized pairwise from boiling EtOH and seeded with XXV, give identical racemates. The optical crystalline properties of XXIII, XXIV, and XXV are given. Hydrogenation of 6 g. III in 50 cc. EtOH and 100 cc. N HCl with PtO2 gives almost 100% (+)-hexahydrophenyltetrahydrothebaimine (XXVI), slender prisms, m. 129-30.5°, [α]D28 -8.5° (c 0.73, EtOH). XXVI, [α]D25 -9° (c 1.0, EtOH), is also obtained when IV or XXIII is hydrogenated under the same conditions (HCl salt, slender prisms, m. 253-5° (decomposition), [α]D28 -17.6° (c 0.25, EtOH)). N-Methomethiodide (XXVIa) is prepared in 41% yield, m. 231-2.5°, [α]D29 -4.8° (c 0.31, EtOH), in addition to 46% of the HI salt of unchanged XXVI. Degradation of XXVIa with EtONa gives (+)-vinylhexahydrophenyltetrahydrothebaol, needles, crystallizing with 0.25 H2O, m. 75.5-7°, [α]D29 -22.7° (c 0.33, AcOEt). It gives an orange-red dye with diazotized PhNH2 and an Ac derivative, m. 79-80.5°, [α]D28 -26.6° (c 0.23, AcOEt). Reduction of V like IV gives (-)-hexahydrophenyltetrahydrothebaimine (XXVII), m. 128-9.5°, [α]D25 10.0° (c 0.90, EtOH); N-methomethiodide (XXVIIa), m. 231-2°, [α]D25 6.6° (c 0.60, EtOH), on degradation gives (-)-vinylhexahydrophenyltetrahydrothebaol, m. 70-5°, [α]D26 35.4°, which is not quite pure. Degradation of XXIIIa with EtONa gives 72% (+)-vinylphenyltetrahydrothebaol, m. 85.5-7°, [α]D29 -58.7° (c 0.43, EtOH); Ac derivative, rectangular prisms, m. 102-4°, [α]D28 -48.5° (c 0.27, AcOEt), when reduced with PtO2 in AcOEt containing AcOH gives acetylethylphenylhexahydrothebaol, m. 80°, [α]D25 -29° (c 0.31, AcOEt), identical with XIV. Refluxing 12 g. III with 40 cc. 48% HBr 0.5 h. gives 85% norphenyldihydrothebaine-HBr, crystallizing with 3 H2O, m. 200-10°, [α]D20 31.4° (c 0.4, EtOH); free base (XXVIII), crystallizing with 0.5 H2O, m. 130-6°, [α]D29 12.3° (c 0.3, EtOH). XXVIII with CH2N2 gives phenyldihydrothebaine Me ether; HBr salt (XXIX) m. 86.5-9° (decomposition), [α]D28 21.4° (c 0.34, EtOH); methiodide m. 195-7°, [α]D28 19.2° (c 0.34, EtOH). Attempts to prepare an oxime of XXVIII failed. Methylation of III with CH2N2 and treatment of the reaction product with HBr give XXIX, m. 86-8°, [α]D28 21.9° (c 0.33, EtOH). When a suspension of 3.3 g. methyldihydrothebainone methiodide is boiled 15 min. with 30% KOH 66% methyldihydrothebainonemethine, felted needles, m. 164-5° (darkening), [α]D20 163° (c 1.0, EtOH), is formed; methiodide (XXX), m. 246-9° (evacuated tube), [α]D20 117° (c 0.51, EtOH). Degradation of XXX by boiling it with 30% KOH gives 88% methyldehydrothebenone, subliming 150°/0.1 mm., m. 183-4°, [α]D20 262° (c 0.52, Me2CO), which gives a neg. test with VI. Alkaline degradation of isomethyldihydrothebainone-MeI gives isomethyldihydrothebainonemethine (XXXI), m. 193°, [α]D20 231° (c 0.2, EtOH), which gives an intense red color with VI. When the methiodide of XXXI is degraded with KOH, isomethyldehydrothebenone, m. 116.5-17°, [α]D20 252° (c 0.49, EtOH), is isolated in poor yield and gives a neg. test with VI. The x-ray diffraction patterns of IIIb, XXIb, IV, V, a mixture of IV and V, XXIII, XXIV, and a mixture of XXIII and XXIV are given; UV absorption curves of III, VIII, and some other thebaine derivs. are shown. The great stability of the ring system, the retention of the vinyl group in the final step of exhaustive methylation, and other peculiarities of I are inexplicable on the basis of the accepted thebaine formula, and since thebaine is related to morphine through dihydromorphine diMe ether, this also casts doubt on the structure of morphine.

AN 1948:8772 HCAPLUS <<LOGINID::20080722>>
DN 42:8772

OREF 42:1944b-i,1945a-i,1946a-i,1947a-f
TI The phenyldihydrothebaines
AU Small, Lyndon; Sargent, Lewis J.; Bralley, James A.
CS Natl. Inst. of Health, Bethesda, MD
SO Journal of Organic Chemistry (1947), 12, 839-68
CODEN: JOCEAH; ISSN: 0022-3263
DT Journal
LA Unavailable
OS CASREACT 42:8772

L6 ANSWER 8 OF 12 HCAPLUS COPYRIGHT 2008 ACS on STN
TI The Products of Hydrolysis of α-Chloromorphide
AB By hydrolysis of α-chloromorphide, Schryver and Lees (J. Chemical Society, 77, 1024) obtained β-isomorphine together with the hydrochloride of a base that was subsequently named neoisomorphine by Lees (Proc. Chemical Society, 23, 200; C. A., 1907, 845) and γ-isomorphine by Knorr (Ber., 40, 3846; C. A., 1908, 114). The author shows that besides β-isomorphine and γ-isomorphine, the mixture of bases obtained in the hydrolysis of α-chloromorphide also contains α-isomorphine, which can be isolated by treating the mixture with Me2CO. In preparing α-chloromorphide by Schryver and Lees's method, it is best to take a good excess of POCl3 as the reaction is facilitated by thinning the liquid. To add CHCl3 for the same purpose is not advisable, as this gives rise to formation of alkyl phosphites. For the same reason the excess of POCl3 should be removed by throwing the reaction product on ice instead of EtOH. γ-Isomorphine hydrochloride, shining prisms, easily soluble in H2O, very difficultly in EtOH, m. 314° with decomposition; [α]D15 -76° (-79.1°, Lees). Hydrobromide, hard crystals, solubility same as preceding, m. 298°; [α]D15 -71° (c=1.885, in H2O). The methiodide decomposes at 293° (m. 297°, Lees); [α]D15 -50° (-54.5° Lees). By boiling γ-isomorphine with Ac2O, an oily diacetyl derivative was obtained which was converted into a methiodide, C22H26NO5I; needles m. about 267° with decomposition, moderately soluble in H2O, slightly soluble in MeOH and still less in EtOH; [α]D15 -24° (c=1.273 in H2O). For comparison the methiodide of diacetylmorphine was made; needles, m. about 252° with decomposition. [α]D15 -107° (c=0.896 in H2O). Rotation of diacetylmorphine is -166° (c=1.24 in MeOH). By warming γ-isomorphine with MeI and MeONa it was converted into pseudocodeine methiodide; nacreous leaflets, m. 278-9° with decomposition ; [α]D15 -50.6° (c=1.325 in H2O).
AN 1908:8733 HCAPLUS <<LOGINID::20080722>>
DN 2:8733
OREF 2:1974g-i,1975a-b
TI The Products of Hydrolysis of α-Chloromorphide
AU Oppe, Alfred
CS Chem. Inst.;Univ. Jena.
SO Berichte der Deutschen Chemischen Gesellschaft (1908), 41, 975-81
CODEN: BDCGAS; ISSN: 0365-9496
DT Journal
LA Unavailable

L6 ANSWER 9 OF 12 HCAPLUS COPYRIGHT 2008 ACS on STN
TI Action of Halogen on Morphine Derivatives. II
AB Further investigation of the action of Br on α-methylmorphimethine showed that, contrary to the previous statement (Ibid., 40, 2828; C. A., 1907, 237), hydroxybromdihydro-α-methylmorphimethine, the product of bromination in CHCl3 solution, when heated with acetic anhydride, yields

the same 3-methyl-4,6-diacetyltrihydroxyphenanthrene as is obtained under the same conditions from acetoxybromdihydro-α-methylmorphimethine, the bromination product in glacial acetic acid solution. The same phenanthrene derivative is also obtained from the dibromide of acetyl-α-methylmorphimethine which the authors obtained (as a hydrobromide) by brominating acetyl-α-methylmorphimethine in either $CHCl_3$ or glacial acetic acid solution and which easily loses a mol of HBr changing to a monobrom compound. The formation of this unstable dibromide indicates that in all 3 cases the reaction consists in the addition of 2 Br atoms, one of which is then exchanged for an OH in the hydroxybromdihydro-α-methylmorphimethine and for a $CH_3.COO$ group in the acetoxybromdihydro-α-methylmorphimethine. On boiling the latter with dilute acetic acid it loses a mol. of HBr and is converted into a compound of a phenolic character. This shows that the Br atom in acetoxybromdihydro-α-methylmorphimethine must be in ring III containing the CH.OH group which is converted into a phenolic OH. One of the 2 Br atoms must, therefore, in all three cases adds itself to ring III in position 8, while the second must be either in the same ring at the other end of the double union, or assuming with Knorr the presence of a conjugated double union in α-methylmorphimethine, at 10. α-Methylmorphimethine (Knorr). α-Methylmorphimethinedibromide. The Br in 10 is exchanged for either OH or $CH_3.COO$ in the above-mentioned compounds. That the Br atoms are not taken up at 9 and 10 is also shown by the fact that the three brominated compounds, when heated with acetic anhydride, give 3-methyl-4,6-diacetyltrihydroxyphenanthrene and not 3-methyl-4,9((10)-diacetyltrihydroxyphenanthrene which is obtained from Pschorr's dichloride (Ibid., 39, 3130) and Knorr's 9(10)-ketodihydromethylmorphimethine. On warming acetoxybromdihydro-α-methylmorphimethine with acetic anhydride, the authors obtained the bromide of an ammonium base which was named nor-p-thebainebrommethylate. Acetoxybromdihydro-α-methylmorphimethine. Nor-p-thebainebrommethylate. The presence of sod. acetate prevents the formation of the ammonium base. Instead of the latter, the difficultly soluble salt of acetoxyacetyl-α-methylmorphimethine is formed. Neither could an ammonium base be obtained from the acetyldibromdihydro-α-methylmorphimethine (dibromide of acetyl-α-methylmorphimethine). Instead of the ammonium base, a hydrobromide of an acetylbrommethylmorphimethine was obtained which was not identical with the compound obtained by boiling the hydrobromide of acetyldibromdihydro-α-methylmorphimethine with H_2O. No dibromide could be obtained by brominating acetyl-β-methylmorphimethine in glacial acetic acid solution. Acetyldibromdihydro-α-Melhylmorphimethine hydrobromide, $C_{21}H_{25}Br_2NO_4.HBr$ (from acetyl α-methylmorphimethine and Br in $CHCl_3$ or glacial acetic acid). In concentrated solutions the yield is almost quantitative; in dilute solutions, only 0.5 of the theoretical amount is obtained. The HBr comes partly at least from the dibromide, part of which loses acid and is converted into a monobrom compound; fine crystals, m. 202° with decomposition; very difficultly soluble in H_2O, insoluble in ether or $CHCl_3$. Cold Na_2CO_3 solution sets the base free from the solution of its salts; if quickly shaken out with ether in presence of Na_3CO_3 the free base can be obtained and converted into a picrate; on standing in ethereal solution or by evaporation of the ether the base loses one mol. HBr and is converted into the hydrobromide of acetylbrom -α-methylmorphimethine, $C_{21}H_{24}BrNO_4HBr$. The same transformation can be easily effected by boiling the hydrobromide of acetyldibromdihydro-α-methylmorphimethine with H_2O. The acetylbrom-β-methylmorphimethine was not isolated, but was converted into the chlorplatinate, $(C_{19}H_{21}BrNO_4)_2H_2PtCl_6.2H_2O$. By saponifying the hydrobromide of acetylbrom-α-methylmorphimethine with Na methylate, brom-α-methylmorphimethine, was obtained and converted

into the chlorplatitnate, (C19H22BrNO3)2H2Pt6Cl, and iodomethylate, C19H22BrNO3CH3I. A simple elimination of the acetyl group from th hydrobromides of either acetyldibromdihydro-α-methylmorphimethine of acetylbrom-α-methylmorphimethine could not be effected: in both cases Br-free phenanthrene derivatives were obtained. Acetylbromiso-α-methylmorphimethine hydrobromide, C21H24.BrNO4.HBr (by boiling acetyldibromdihydro-α-methylmorphimethine with acetic anhydride for a short time); shining needles (from H2O), decompose 235°. KI converts it into the corresponding HI salt; needles, decomposes 222°. Alkali carbonates liberate the free base, which is soluble in ether and differs from the isomeric acetylbrom-α-methylmorphimethine in being more easily soluble and forming more easily crystallizable salts with the halogen acids. Acetylnor-p-thebaine brommethylate, C21H4BrNO4 (by heating acetoxybromdihydro-α-methylmorphimethine with acetic anhydride to 120-30° for a short time); separates from H2O in concentrically grouped needles which change to compact prisms within 24 hrs.; m. 231-2°; dissolves without color in H2SO4. Cold dilute alkali does not precipitate the ammonium base; concentrated alkali salts it out unchanged. KI precipitates the difficultly soluble iodomethylate, m. 236°. Ag2O converts the bromand iodomethylates into the strongly alkaline ammonium base in which, upon standing for 24 hrs. in the cold or quickly upon boiling, the acetyl group in 6 is saponified with formation of a neutral salt (the acetate) which is converted by KI into the difficultly soluble n-p-thebaine iodomethylate, C20H22NO3I; m. 220°. Addition of Ag2O to the solution of the latter gives a permanently alkaline liquid which, upon concentration, deposits a flocculent amorphous base which becomes brown in the air, is easily soluble in CHCl3, difficultly in ether, and forms an amorphous iodomethylate of a low m. As this iodomethylate is not identical with the one from which it is formed (m. 220°), there could not have been a simple splitting off of CH3.OH from the ammonium base. Most probably the N ring is opened in the reaction with elimination of a mol. H2O and formation of a methine base. The same methine base is formed by boiling acetyl nor-p-thebaine brommethylate with a 30% solution of NaOH.

AN 1908:1589 HCAPLUS <<LOGINID::20080722>>
DN 2:1589
OREF 2:414a-i,415a-h
TI Action of Halogen on Morphine Derivatives. II
AU Vongerichten, E.; Densdorff, O.
CS Techno-Chem. Inst.;Univ. Jena
SO Berichte der Deutschen Chemischen Gesellschaft (1908), 40, 4146-54
CODEN: BDCGAS; ISSN: 0365-9496
DT Journal
LA Unavailable

L6 ANSWER 10 OF 12 HCAPLUS COPYRIGHT 2008 ACS on STN
TI Action of Halogen on Morphine Derivatives
AB The action of halogen on morphine or codeine is different from that on α- and β-methylmorphimethine. On the other hand dihydro-α- and dihydro-β-methylmorphimethine behave towards halogen exactly like morphine or codeine. When morphine or codeine is treated with bromine, substitution products are obtained in which the bromine is attached to that ring which in morphine contains the phenolic hydroxyl, not to one of the "bridge" carbon atoms of the phenanthrene nucleus. In the same way from dihydro-α and dihydro-β-methylmorphimethine, when acted upon by bromine either in chloroform or glacial acetic acid solution, monobrom-substitution products are formed similar to those obtained from morphine or codeine, while the action of bromine upon methylmorphimethine is different in

different solvents. In chloroform solution, α-methylmorphimethine, when acted upon by bromine, yields a hydroxydihydrobrommethylmorphimethine which when heated with acetic anhydride, gives as one of the decomposition products the same brommorphol as is formed under the same conditions from bromcodeine. Hence the bromine atom in the hydroxydihydrobromethylmorphimethine is not attached to one of the "bridge" carbon atoms. But when the action of bromine or either α- or β-mthylmorphimethine takes place in glacial acetic acid solution, an acetoxybromdihydromethylmorphimethine is obtained which is formed by the addition of two bromine atoms to the "bridge" carbon atoms and the subsequent replacement of one of the bromine atoms by the group CH3CO2. The acetoxybromdihydromethylmorphimethine from α-methylmorphimethine was obtained in crystalline form, while the corresponding compound from β-methylmorphimethine could not be obtained in pure condition. Hydroxydihydrobrom-α-methylmorphimethine C13H24BrNO4, (from α-methylmorphimethine and bromine in alcohol-free chloroform) stellate leaflets (from methyl alcohol), m. 170°, loses H2O at 180°. Concentrated sulphuric acid dissolves it with a brown-red color. Upon careful addition of water the liquid at first becomes brownish green and then dirty brownish blue. When warmed with dilute sulphuric acid the compound does not lose HBr. On boiling the compound with methyl iodide in methyl alcoholic solution a crystalline iodomethylate is formed which decomposes at 150°. Heated for 15 hrs. to 180° with acetic anhydride the compound yields brommorphol. Acetoxybromdihydro-α-methylmorphimethine, C22H26BrNO4 (from α-methylmorphimethine and bromine in glacial acetic acid), crystallizes with one mol. of benzene of crystallization, m. 118-138°. The compound is very unstable, beginning to decompose and giving off HBr when warmed with water to 60-80°. Heated above its m. p. the compound loses both water and acetic acid. At 100° it is changed to a hydrobromide from which a tertiary base precipitates upon addition of ammonia. With methyl iodide in chloroform solution the compound combines to an oily but gradually soldifying iodomethylate. Heated with acetic anhydride, it gives diacetylmethyltrihydroxyphenanthrene, previously obtained from codeinone by Knorr (Ibid., 36, 3081). On heating brom-α-methylmorphimethine (from brommorphine) to 180° in a current of hydrogen, it is changed to the isomeric brom-β-methylmorphimethine, m. 184°; [α]215 =+128.22° (in alcohol 99%; c=0.7128). Brom-α-methylmorphimethine is levorotatory; [α]215 =-104.06° (in alcohol 99%; c=1.2252). Brom-β-methylmorphimethine gives an amorphous iodomethylate which is dextrorotatory, while the iodomethylate of brom-α-methylmorphimethine is levorotatory; [α]215=-110.71° (c=0.56). Bromdihydro-α-methylmorphimethine, C19H24BrNO3, (from dihydro-α-methylmorphimethine and bromine in either chloroform or glacial acetic acid); m. 165°. Iodomethylate, C19H24BrNO2.CH2I, (from components in chloroform solution); m. 264°. Bromdihydro-β-methylmorphimethine (by same method as the α-compound), m. 169°. Iodomethylate, m. 277°. When the iodomethylate of the α-compound is boiled with strong sodium hydroxide it is converted into the iodomethylate of the β-compound.

AN 1907:9887 HCAPLUS <<LOGINID::20080722>>
DN 1:9887
OREF 1:2371e-i,2372a-f
TI Action of Halogen on Morphine Derivatives
AU Vongerichten, E.; Huebner, O.
CS Techn. Chem. Inst., Univ. Jena
SO Berichte der Deutschen Chemischen Gesellschaft (1907), 40, 2827-31
CODEN: BDCGAS; ISSN: 0365-9496

DT Journal
LA Unavailable

L6 ANSWER 11 OF 12 HCAPLUS COPYRIGHT 2008 ACS on STN
TI Contribution to Our Knowledge of Morphine. XI. Communication. Note on Oxy-Methylmorphimethine (Ketodihydromethylmorphimethine)
GI For diagram(s), see printed CA Issue.
AB A renewed investigation of the substance previously obtained by exhaustive methylation of hydroxy-codeine, and named hydroxymethylmorphimethine (Ber., 39, 1414), showed that contrary to former statements the substance was not a divalent alcohol but that it contained one alcoholic OH and one CO group. The formation of a ketone from hydroxycodeine which contains two alcoholic OH groups is similar to the transformation of cinchonine iodomethylate to methylcinchotoxine or narcotine iodomethylate to narceine, i. e., the reaction consists in the change of the group CO.CH2.+N(CH3)2CH2. In accord with this, the name of the substance is changed to ketodihydromethylmorphimethine. As Pschorr's pvridine formula for morphine (Ber., 35, 4382) does not account for the change of an alcoholic OH to a ketone group, the authors propose for morphine a modified formula which contains a coumarone ring, and in which the middle benzine ring, containing no double linkings, behaves like an aliphatic group. The peculiar transformation of hydroxycodeine into ketodihydromethylmorphimethine could be best explained by assuming that the phenanthrene nucleus does not exist as such in the morphine alkaloids, but is formed only during their decomposition. Hydriodide of monacetylketodihydromethylmorphimeth ine, C21H25NO8.HI; fine, white, pliable needles (from hot water) m. about 270° with decomposition. Hydrobromide, C21H23NO8.HBr, fine needles, by quick cooling; quadratic leaflets, by slow cooling; decomposes 280-285°. The difference between the mono- and diacetyl compound is so small that the data had been erroneously interpreted for a diacetyl derivative.
AN 1907:8799 HCAPLUS <<LOGINID::20080722>>
DN 1:8799
OREF 1:2126d-i,2127a-d
TI Contribution to Our Knowledge of Morphine. XI. Communication. Note on Oxy-Methylmorphimethine (Ketodihydromethylmorphimethine)
AU Knorr, Ludwig; Horlein, Heinrich
CS Chem. Inst Univ. Jena
SO Berichte der Deutschen Chemischen Gesellschaft (1907), 40, 2042-48
CODEN: BDCGAS; ISSN: 0365-9496
DT Journal
LA Unavailable

L6 ANSWER 12 OF 12 HCAPLUS COPYRIGHT 2008 ACS on STN
TI Halogen derivatives of morphine and codeine, and their degradation
AB Chloromorphide results from the action of hydrogen chloride on morphine at ordinary temperature and melts at 192°; the methiodide melts at 207°. The preparation, melting point, boiling point, crystallization, decomposition, and color reaction of other halogen derivatives of morphine and codeine are presented. These include bromomorphide hydrobromide, bisthiomorphide, dichloromethylmorphimethine, and benzoylcodeine methiodide.
AN 1906:124369 HCAPLUS <<LOGINID::20080722>>
DN 0:124369
TI Halogen derivatives of morphine and codeine, and their degradation
AU Pschorr, Robert; Vogtherr, Hermann; Kuhtz, E.; Roth, Heinrich
SO Berichte der Deutschen Chemischen Gesellschaft (1906), 39,

```
     3130-9
     From: J. Chem. Soc.,  Abstr. 90, I, 877-8 1906
     CODEN: BDCGAS
DT   Journal
LA   Unavailable


=> d his

     (FILE 'HOME' ENTERED AT 08:08:59 ON 22 JUL 2008)

     FILE 'HCAPLUS' ENTERED AT 08:11:09 ON 22 JUL 2008
L1         43846 S MORPHINE
L2         13888 S HYDROBROMIDE
L3        948385 S STABILITY OR (SHELF LIFE) OR DECOMPOSITION
L4            14 S L1 AND L2 AND L3
L5           530 S L2 AND L3
L6            12 S L4 AND (PY<2003 OR AY<2003 OR PRY<2003)
L7           357 S L5 AND (PY<2003 OR AY<2003 OR PRY<2003)

     FILE 'STNGUIDE' ENTERED AT 08:11:21 ON 22 JUL 2008

     FILE 'HCAPLUS' ENTERED AT 08:11:28 ON 22 JUL 2008

     FILE 'STNGUIDE' ENTERED AT 08:11:29 ON 22 JUL 2008

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CA SUBSCRIBER PRICE                                       0.00      -9.60
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DICTIONARY FILE UPDATES:  20 JUL 2008  HIGHEST RN 1035004-20-6

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http://www.cas.org/support/stngen/stndoc/properties.html

=> exp morphine-6-glucuronide/cn
E1            1     MORPHINE-6-B-D-GLUCURONIDE HYDROBROMIDE/CN
E2            1     MORPHINE-6-3H/CN
E3            0 --> MORPHINE-6-GLUCURONIDE/CN
E4            1     MORPHINE-6-SUCCINATE/CN
E5            1     MORPHINE-6-SULFONIC ACID/CN
E6            1     MORPHINE-7,8-T2, 7,8-DIHYDRO-/CN
E7            1     MORPHINE-ACETAMINOPHEN MIXTURE/CN
E8            1     MORPHINE-ALPRENOLOL MIXT./CN
E9            1     MORPHINE-FLUPIRTINE MIXT./CN
E10           1     MORPHINE-METHYL-D3/CN
E11           1     MORPHINE-N-(METHYL-D3) HYDROCHLORIDE/CN
E12           1     MORPHINE-N-CT3/CN

=> exp 6-glucuronomorphine/cn
E1            1     6-GERMATRICYCLO(3.1.0.02,6)HEX-3-EN-6-YLIUM, 2-METHYL-, (DEL
                    OC-1,2,3,4,5,6)-/CN
E2            1     6-GINGESULFONIC ACID/CN
E3            0 --> 6-GLUCURONOMORPHINE/CN
E4            1     6-GLUTATHIONYL QUERCETIN/CN
E5            1     6-GLY-1-10-GAP-43/CN
E6            1     6-GLYCINAMIDE-3-CHLOROPHENYLARSONIC ACID/CN
E7            1     6-GLYCINE-5-(L-TYROSINE)-BRADYKININ/CN
E8            1     6-GLYCINE-8-(B-CYCLOHEXYL-L-LACTIC ACID)-BRADYKININ/CN
E9            1     6-GLYCINE-8-(B-PHENYL-L-LACTIC ACID)-BRADYKININ/CN
E10           1     6-GLYCINE-8-(L-TYROSINE)-BRADYKININ/CN
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E11           1     6-GLYCINEBRADYKININ/CN
E12           1     6-GLYCOLYL BRADYKININ MONOACETATE/CN

=> exp morphine/cn
E1            1     MORPHINANOL, BROMO-3-METHOXY-17-METHYL-4-PHENOXY-, HYDROCHLO
                    RIDE/CN
E2            1     MORPHINANTRIOL, 4,5-EPOXY-3-METHOXY-17-METHYL-, (5A,6.
                    ALPHA.)-/CN
E3            1 --> MORPHINE/CN
E4            1     MORPHINE 2,3-DIHYDRODIOL/CN
E5            1     MORPHINE 2-THIENYLGLYCOLATE/CN
E6            1     MORPHINE 3,6-BIS(TRI-O-ACETYLGLUCURONIDE) DIMETHYL ESTER/CN
E7            1     MORPHINE 3,6-BIS(TRI-O-ISOBUTYRYLGLUCURONIDE) DIMETHYL ESTER
                    /CN
E8            1     MORPHINE 3,6-DI-B-D-GLUCURONIDE/CN
E9            1     MORPHINE 3,6-DIBUTYRATE/CN
E10           1     MORPHINE 3,6-DIGLUCURONIDE/CN
E11           1     MORPHINE 3,6-DINICOTINATE-CARBOXYL-14C/CN
E12           1     MORPHINE 3-((1,1'-BIPHENYL)-2-CARBOXYLATE)/CN

=> exp morphine 6-gluc/cn
E1            1     MORPHINE 6-DEHYDROGENASE, CONJECTURAL (PYROBACULUM AEROPHILU
                    M STRAIN IM2 GENE PAE3247)/CN
E2            1     MORPHINE 6-FORMATE/CN
E3            0 --> MORPHINE 6-GLUC/CN
E4            1     MORPHINE 6-GLUCURONIDE/CN
E5            1     MORPHINE 6-GLUCURONIDE HYDROCHLORIDE/CN
E6            1     MORPHINE 6-HEMISUCCINATE/CN
E7            1     MORPHINE 6-HEXANOATE/CN
E8            1     MORPHINE 6-ISOBUTYRATE/CN
E9            1     MORPHINE 6-METHYL ETHER/CN
E10           1     MORPHINE 6-NICOTINATE L-TARTRATE/CN
E11           1     MORPHINE 6-O-A-GLUCURONIDE/CN
E12           1     MORPHINE 6-O-GLUCURONIDE/CN

=> s E4-#5
LEFT TRUNCATION IGNORED FOR FILE 'REGISTRY'
          3608 E4
      15258955 5
L8          36 E4-#5
                 (E4(W)#5)
Left truncation is not valid in the specified search field in the
specified file.  The term has been searched without left truncation.
Examples: '?TERPEN?' would be searched as 'TERPEN?' and '?FLAVONOID'
would be searched as 'FLAVONOID.'

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used a truncation symbol after a punctuation mark, the system may
interpret the truncation symbol as being at the beginning of a term.
Implied proximity is used in search fields indexed as single words,
for example, the Basic Index.

=> s E4-E5
              1 "MORPHINE 6-GLUCURONIDE"/CN
              1 "MORPHINE 6-GLUCURONIDE HYDROCHLORIDE"/CN
L9            2 ("MORPHINE 6-GLUCURONIDE"/CN OR "MORPHINE 6-GLUCURONIDE HYDROCHL
                ORIDE"/CN)

=> d his

     (FILE 'HOME' ENTERED AT 08:08:59 ON 22 JUL 2008)
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     FILE 'HCAPLUS' ENTERED AT 08:11:09 ON 22 JUL 2008
L1         43846 S MORPHINE
L2         13888 S HYDROBROMIDE
L3        948385 S STABILITY OR (SHELF LIFE) OR DECOMPOSITION
L4            14 S L1 AND L2 AND L3
L5           530 S L2 AND L3
L6            12 S L4 AND (PY<2003 OR AY<2003 OR PRY<2003)
L7           357 S L5 AND (PY<2003 OR AY<2003 OR PRY<2003)

     FILE 'STNGUIDE' ENTERED AT 08:11:21 ON 22 JUL 2008

     FILE 'HCAPLUS' ENTERED AT 08:11:28 ON 22 JUL 2008

     FILE 'STNGUIDE' ENTERED AT 08:11:29 ON 22 JUL 2008

     FILE 'REGISTRY' ENTERED AT 08:33:00 ON 22 JUL 2008
                EXP MORPHINE-6-GLUCURONIDE/CN
                EXP 6-GLUCURONOMORPHINE/CN
                EXP MORPHINE/CN
                EXP MORPHINE 6-GLUC/CN
L8            36 S E4-#5
L9             2 S E4-E5

=> file hcaplus
COST IN U.S. DOLLARS                            SINCE FILE      TOTAL
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FULL ESTIMATED COST                                 21.98      63.24

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)      SINCE FILE      TOTAL
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CA SUBSCRIBER PRICE                                  0.00      -9.60

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FILE COVERS 1907 - 22 Jul 2008  VOL 149 ISS 4
FILE LAST UPDATED: 20 Jul 2008  (20080720/ED)

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reclassification data for the second quarter of 2008.

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=> s l9
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L10        612 L9

=> s bromide or hydrobromide
         296727 BROMIDE
          13888 HYDROBROMIDE
L11      307371 BROMIDE OR HYDROBROMIDE

=> s l10 and l11
L12          21 L10 AND L11

=> s l12 and (PY<2003 or AY<2003 or pRY<2003)
       22935598 PY<2003
        4491924 AY<2003
        3960009 PRY<2003
L13          11 L12 AND (PY<2003 OR AY<2003 OR PRY<2003)

=> file stnguide
COST IN U.S. DOLLARS                            SINCE FILE      TOTAL
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FULL ESTIMATED COST                                   2.69      65.93

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)      SINCE FILE      TOTAL
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CA SUBSCRIBER PRICE                                   0.00      -9.60

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LAST RELOADED: Jul 18, 2008 (20080718/UP).

=> d l13 1-11 ti abs bib
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L13  ANSWER 1 OF 11  HCAPLUS  COPYRIGHT 2008 ACS on STN
TI   Specific haplotypes of MDR1 gene and their use in diagnosis and therapy
AB   The invention relates to specific combinations of SNPs of the MDR1 gene
     (haplotypes), and to their use for individualizing drug therapy and for
     predicting the risk of tumor diseases in humans.  Thus, specific
     combinations of 5 SNPs of the MDR1 gene, i.e., (1) exon 6 +139:
     C→T, (2) cDNA 1236: C→T, (3) exon 17 -76: T→A, (4)
     cDNA 2677: G→T or G→A, and (5) cDNA 3435: C→T, were
     associated with colorectal carcinoma.  These SNPs were determined by PCR-RFLP.
     The carcinoma-associated haplotypes corresponded to alterations in digoxin
     transport by the P glycoprotein.
AN   2004:413100  HCAPLUS <<LOGINID::20080722>>
DN   140:418948
TI   Specific haplotypes of MDR1 gene and their use in diagnosis and therapy
IN   Gaikovitch, Elena; Johne, Andreas; Koepke, Karla; Roots, Ivar
PA   Charite-Universitaetsme Dizin Berlin, Germany
SO   PCT Int. Appl., 58 pp.
     CODEN: PIXXD2
DT   Patent
LA   German
FAN.CNT 1
     PATENT NO.          KIND   DATE        APPLICATION NO.        DATE
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PI WO 2004042081 A1 20040521 WO 2003-EP12294 20031104 <--
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
AU 2003280867 A1 20040607 AU 2003-280867 20031104 <--
PRAI DE 2002-10251236 A 20021104 <--
WO 2003-EP12294 W 20031104
RE.CNT 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 2 OF 11 HCAPLUS COPYRIGHT 2008 ACS on STN
TI Morphine-6-glucuronide salts and stability thereof
AB Several salts of morphine-6-glucuronide are prepared, and the hydrobromide salt (M6G.HBr) is surprisingly stable compared to other M6G salts and M6G free base. Use of M6G.HBr as a medicament, in particular as an analgesic, and methods of making M6G.HBr are described.
AN 2004:162705 HCAPLUS <<LOGINID::20080722>>
DN 140:205122
TI Morphine-6-glucuronide salts and stability thereof
IN Graham, John Aitken
PA Cenes Limited, UK
SO PCT Int. Appl., 27 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2004016633	A1	20040226	WO 2003-GB3562	20030814 <--
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2494812	A1	20040226	CA 2003-2494812	20030814 <--
AU 2003255790	A1	20040303	AU 2003-255790	20030814 <--
EP 1537132	A1	20050608	EP 2003-787894	20030814 <--
EP 1537132	B1	20060104		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
JP 2006500360	T	20060105	JP 2004-528672	20030814 <--
AT 315041	T	20060215	AT 2003-787894	20030814 <--
ES 2256790	T3	20060716	ES 2003-787894	20030814 <--
ZA 2005001053	A	20050829	ZA 2005-1053	20050204 <--
IN 2005CN00181	A	20070907	IN 2005-CN181	20050214 <--
NO 2005001261	A	20050311	NO 2005-1261	20050311 <--
US 20060166900	A1	20060727	US 2005-524149	20050628 <--
PRAI GB 2002-18811	A	20020814 <--		
WO 2003-GB3562	W	20030814		

RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 3 OF 11 HCAPLUS COPYRIGHT 2008 ACS on STN
TI Method and pharmaceutical composition using devazepide and surfactant with opioid analgesic therapy
AB There is described a method of treatment of a patient requiring analgesia which comprises the sep., simultaneous or sequential administration of a therapeutically effective amount of an opioid analgesic, devazepide and a surfactant. There is also described a monophasic pharmaceutical composition comprising an amount of devazepide effective in the enhancement of opioid analgesia and a pharmaceutically acceptable surfactant. The use of a surfactant is advantageous in that it improves the powder flow and/or separation properties of solid devazepide and also reduces or mitigates the undesirable side effects of opioid administration, e.g. constipation.
AN 2003:633285 HCAPLUS <<LOGINID::20080722>>
DN 139:159955
TI Method and pharmaceutical composition using devazepide and surfactant with opioid analgesic therapy
IN Jackson, Karen
PA ML Laboratories PLC, UK
SO U.S. Pat. Appl. Publ., 8 pp., Cont.-in-part of U.S. Ser. No. 108,659.
CODEN: USXXCO
DT Patent
LA English
FAN.CNT 8

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 20030153592	A1	20030814	US 2003-349431	20030122 <--
	US 6713470	B2	20040330		
	US 20040198723	A1	20041007	US 2002-53962	20020122 <--
	US 20030139396	A1	20030724	US 2002-108659	20020327 <--
	US 20040043990	A1	20040304	US 2003-410311	20030409 <--
	US 20040167146	A1	20040826	US 2003-622492	20030721 <--
	US 20040142959	A1	20040722	US 2004-752411	20040107 <--
	US 20080125414	A1	20080529	US 2007-852727	20070910 <--
PRAI	US 2002-53962	B2	20020122 <--		
	US 2002-108659	A2	20020327 <--		
	GB 2002-1367	A	20020122 <--		
	GB 2002-8129	A	20020409 <--		
	US 2003-349431	A2	20030122		
	US 2003-622492	A2	20030721		

L13 ANSWER 4 OF 11 HCAPLUS COPYRIGHT 2008 ACS on STN
TI Method of treatment of patients requiring analgesia with opioid analgesics
AB There is described a method of treatment of a patient requiring analgesia which comprises the sep., simultaneous or sequential administration of a therapeutically effective amount of an opioid analgesic, devazepide, and a surfactant. There is also described a monophasic pharmaceutical composition comprising devazepide effective in the enhancement of opioid analgesia and a surfactant. The daily dosage of devazepide is up to 0.7 mg/kg/day.
AN 2003:590987 HCAPLUS <<LOGINID::20080722>>
DN 139:138761
TI Method of treatment of patients requiring analgesia with opioid analgesics
IN Jackson, Karen
PA Ml Laboratories Plc, UK
SO PCT Int. Appl., 31 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 8

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     PATENT NO.          KIND   DATE        APPLICATION NO.        DATE
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PI   WO 2003061632        A1    20030731    WO 2003-GB221          20030122 <--
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
             CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
             GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
             LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,
             PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ,
             UA, UG, US, UZ, VN, YU, ZA, ZM, ZW
         RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
             KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES,
             FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF,
             BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
     CA 2473884            A1    20030731    CA 2003-2473884        20030122 <--
     EP 1467718            A1    20041020    EP 2003-708305         20030122 <--
     EP 1467718            B1    20051123
         R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
             IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK
     BR 2003007022         A     20041103    BR 2003-7022           20030122 <--
     JP 2005521655         T     20050721    JP 2003-561577         20030122 <--
     AT 310509             T     20051215    AT 2003-708305         20030122 <--
     ES 2253662            T3    20060601    ES 2003-708305         20030122 <--
     NO 2004002758         A     20040922    NO 2004-2758           20040630 <--
     IN 2004KN00923        A     20060512    IN 2004-KN923          20040702 <--
     MX 2004PA07030        A     20041011    MX 2004-PA7030         20040721 <--
PRAI GB 2002-1367          A     20020122  <--
     WO 2003-GB221         W     20030122
RE.CNT  3     THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD
              ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13  ANSWER 5 OF 11  HCAPLUS  COPYRIGHT 2008 ACS on STN
TI   A Computational Ensemble Pharmacophore Model for Identifying Substrates of
     P-Glycoprotein
AB   P-glycoprotein (P-gp) functions as a drug efflux pump, mediating multidrug
     resistance and limiting the efficacy of many drugs.  Clearly,
     identification of potential P-gp substrate liability early in the drug
     discovery process would be advantageous.  We describe a
     multiple-pharmacophore model that can discriminate between substrates and
     nonsubstrates of P-gp with an accuracy of 63%.  The application of this
     filter allows large virtual libraries to be screened efficiently for
     compds. less likely to be transported by P-gp.
AN   2002:227327  HCAPLUS <<LOGINID::20080722>>
DN   137:148
TI   A Computational Ensemble Pharmacophore Model for Identifying Substrates of
     P-Glycoprotein
AU   Penzotti, Julie E.; Lamb, Michelle L.; Evensen, Erik; Grootenhuis, Peter
     D. J.
CS   Deltagen Research Laboratories, San Diego, CA, 92121, USA
SO   Journal of Medicinal Chemistry (2002), 45(9), 1737-1740
     CODEN: JMCMAR; ISSN: 0022-2623
PB   American Chemical Society
DT   Journal
LA   English
RE.CNT  56    THERE ARE 56 CITED REFERENCES AVAILABLE FOR THIS RECORD
              ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13  ANSWER 6 OF 11  HCAPLUS  COPYRIGHT 2008 ACS on STN
TI   Process for preparing morphine-6-glucuronide and its analogues using
     haloglucuronate ester intermediates
GI
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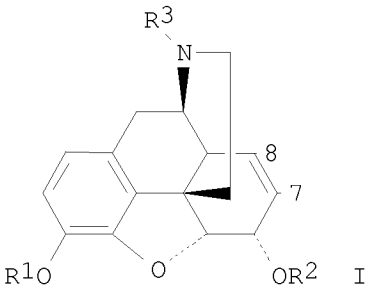

I

AB This invention discloses a process for preparing morphine-6-glucuronide and related compds. (I) [R1 = (un)substituted alkyl, aryl, silyl, acyl; R2 = glycoside ester; R3 = alkyl, aryl, H, (CH2)nX where n is a integer; X = NRR4; R, R4 = H, alkyl, aryl, acyl; C(7) - C(8) linkage is olefin, dihydro, dihydroxy, hydroxyhalo, epoxy, dihalo, hydrohalo, hydrohydroxy, or olefin adducts CHX-CHY; X, Y = epoxy, halogen, hydrohalogen] using haloglucuronate esters as an intermediates in the presence of iodine or an iodonium compound Thus, I (R1 = pivaloyl, R2 = Me β-D-(2,3,4-tripivaloyl)glucuronate, R3 = Me) was prepared by the reaction of 3-O-pivaloylmorphine and 1-deoxy-1-iodo-2,3-4-tri-O-pivaloyl-α-D-glucopyranuronate (also prepared) in presence of iodine.

AN 2000:911257 HCAPLUS <<LOGINID::20080722>>
DN 134:56828

TI Process for preparing morphine-6-glucuronide and its analogues using haloglucuronate ester intermediates

IN Scheinmann, Feodor; Stachulski, Andrew Valentine; Ferguson, John; Law, Jane Louise
PA UFC Limited, UK

SO PCT Int. Appl., 20 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000078764	A1	20001228	WO 2000-GB2232	20000620 <--
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	CA 2375274	A1	20001228	CA 2000-2375274	20000620 <--
	EP 1200441	A1	20020502	EP 2000-938910	20000620 <--
	EP 1200441	B1	20050209		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
	JP 2003502427	T	20030121	JP 2001-504930	20000620 <--
	AT 288917	T	20050215	AT 2000-938910	20000620 <--
	US 6642366	B1	20031104	US 2002-19585	20020607 <--
PRAI	GB 1999-14382	A	19990621 <--		
	WO 2000-GB2232	W	20000620 <--		

OS CASREACT 134:56828; MARPAT 134:56828

RE.CNT 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 7 OF 11 HCAPLUS COPYRIGHT 2008 ACS on STN
TI Synthesis of morphine 6-α-D-glucuronide
AB This paper provides the first report on stereoselective synthesis and characterization of morphine 6-α-D-glucuronide (M6αG), useful as a reference marker for testing the purity and stability of the pharmaceutically important morphine 6-β-D-glucuronide (M6G). The synthesis is based on the glycosylation of 3-O-acetylated morphine with Me 2,3,4-tri-O-acetyl-D-glucopyranosyluronate bromide as glycosyl donor and zinc bromide as catalyst. Furthermore, the authors showed that the α/β stereoselectivity of the reaction can be directed and controlled by the amount of zinc bromide.
AN 2000:595450 HCAPLUS <<LOGINID::20080722>>
DN 133:350433
TI Synthesis of morphine 6-α-D-glucuronide
AU Rukhman, I.; Gutman, A. L.
CS Department of Chemistry, Technion-Israel Institute of Technology, Haifa, 32000, Israel
SO Tetrahedron Letters (2000), 41(35), 6889-6892
CODEN: TELEAY; ISSN: 0040-4039
PB Elsevier Science Ltd.
DT Journal
LA English
OS CASREACT 133:350433
RE.CNT 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 8 OF 11 HCAPLUS COPYRIGHT 2008 ACS on STN
TI The synthesis of some analogs of morphine 6-glucuronide through Wittig reactions upon dihydrocodeinone
AB In preliminary studies to establish the biol. role of the glucuronide unit in morphine 6-glucuronide, a number of codeine derivs. bearing alkyl side chains appended through C-6 have been synthesized using Wittig reactions between suitable ylides and dihydrocodeinone. During the course of this work some aldolization type products of dihydrocodeinone were obtained. Attempts to introduce side chains by radical coupling reactions between bromocodides and allyltributyltin failed.
AN 1998:540981 HCAPLUS <<LOGINID::20080722>>
DN 129:330889
OREF 129:67495a
TI The synthesis of some analogs of morphine 6-glucuronide through Wittig reactions upon dihydrocodeinone
AU Liu, Maxson; Mahon, Mary F.; Sainsbury, Malcolm
CS Department of Chemistry, University of Bath, Claverton Down, Bath, BA2 7AY, UK
SO Journal of the Chemical Society, Perkin Transactions 1: Organic and Bio-Organic Chemistry (1998), (17), 2943-2952
CODEN: JCPRB4; ISSN: 0300-922X
PB Royal Society of Chemistry
DT Journal
LA English
RE.CNT 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 9 OF 11 HCAPLUS COPYRIGHT 2008 ACS on STN
TI A general pattern for substrate recognition by P-glycoprotein
AB P-glycoprotein actively transports a wide variety of chemical diverse compds. out of the cell. Based on a comparison of a hundred compds. previously tested as P-glycoprotein substrates, we suggest that a set of well-defined

structural elements is required for an interaction with P-glycoprotein. The recognition elements are formed by two (type I unit) or three electron donor groups (type II unit) with a fixed spatial separation Type I units consist of two electron donor groups with a spatial separation of 2.5±0.3 Å. Type II units contain either two electron donor groups with a spatial separation of 4.6±0.6 Å or three electron donor groups with a spatial separation of the outer two groups of 4.6±0.6 Å. All mols. that contain at least one type I or one type II unit are predicted to be P-glycoprotein substrates. The binding to P-glycoprotein increases with the strength and the number of electron donor or hydrogen bonding acceptor groups forming the type I and type II units. Correspondingly, a high percentage of amino acids with hydrogen bonding donor side chains is found in the transmembrane sequences of P-glycoprotein relevant for substrate interaction. Mols. that minimally contain one type II unit are predicted to be inducers of P-glycoprotein over-expression.

AN 1998:78980 HCAPLUS <<LOGINID::20080722>>
DN 128:254161
OREF 128:50235a,50238a
TI A general pattern for substrate recognition by P-glycoprotein
AU Seelig, Anna
CS Department of Biophysical Chemistry, Biocenter of the University of Basel, Basel, CH-4056, Switz.
SO European Journal of Biochemistry (1998), 251(1/2), 252-261
CODEN: EJBCAI; ISSN: 0014-2956
PB Springer-Verlag
DT Journal
LA English
RE.CNT 68 THERE ARE 68 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 10 OF 11 HCAPLUS COPYRIGHT 2008 ACS on STN
TI Quantitation of morphine, morphine-3-glucuronide, and morphine-6-glucuronide in plasma and cerebrospinal fluid using solid-phase extraction and high-performance liquid chromatography with electrochemical detection
AB An original, sensitive, and specific high-performance liquid chromatog. (HPLC) assay was developed for the quantitation of morphine and its two major metabolites, morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G), in human plasma and cerebrospinal fluid (CSF) and in rat plasma, using hydromorphone as the internal standard Solid-phase extraction was used to sep. morphine and its glucuronide metabolites from plasma constituents. Extraction efficiencies of morphine, M3G, and M6G from human plasma samples (0.5 mL) were 84, 87, and 88%, resp. Extraction efficiencies of morphine, M3G, and M6G did not differ significantly ($p > 0.05$) between human plasma and CSF or rat plasma. Morphine, M3G, M6G, and hydromorphone were separated on a 10 μ C8 Resolve radially compressed cartridge using a mobile phase comprising methanol:acetonitrile:phosphate buffer, (0.0125M pH 7.5; 10:10:80), in which 11 mg/L of cetyltrimethylammonium bromide (cetrimide) was dissolved. Quantitation was achieved using a single electrochem. detector at ambient temperature (23°C). Standard curves were linear over the ranges 0.020-2.190, 0.027-2.709, and 0.027-0.542 μM for morphine, M3G, and M6G, resp. Lower limits of detection for morphine, M3G, and M6G in human plasma and CSF samples (0.5 mL) were 0.020, 0.027, and 0.027 μM, resp. Corresponding lower limits of detection in rat plasma (0.1 mL) were 0.102, 0.135, and 0.135 μM, resp. Intraassay precision for low and high concns. of morphine, M3G, and M6G were <23 and <8% resp. Similarly, interassay accuracy for low and medium concns. of morphine, M3G, and M6G were <17% and were <9% for high concns.

AN 1994:472903 HCAPLUS <<LOGINID::20080722>>
DN 121:72903
OREF 121:12790h,12791a

TI Quantitation of morphine, morphine-3-glucuronide, and morphine-6-glucuronide in plasma and cerebrospinal fluid using solid-phase extraction and high-performance liquid chromatography with electrochemical detection
AU Wright, Andrew W. E.; Watt, Julie A.; Kennedy, Michelle; Cramond, Tess; Smith, Maree T.
CS R. Brisbane Hosp., Univ. Queensl., Brisbane, 4072, Australia
SO Therapeutic Drug Monitoring (1994), 16(2), 200-8
CODEN: TDMODV; ISSN: 0163-4356
DT Journal
LA English

L13 ANSWER 11 OF 11 HCAPLUS COPYRIGHT 2008 ACS on STN
TI Metabolism of drugs. LX. Synthesis of codeine and morphine glucuronides
AB The first synthesis of 3 glucuronides of narcotics was reported. Codeine D-glucuronide (I) was prepared by the condensation of codeine with the glycosyl bromide (II) in the presence of silver carbonate and the following removal of the protecting groups by solvolysis and hydrolysis with NaOMe and aqueous Ba(OH)2, resp. Morphine 6-D-glucuronide was synthesized similarly to I utilizing 3-acetylmorphine as the starting material. Morphine 3-D-glucoronide (III) was prepared by the condensation of morphine with II in NaOH-acetone. In this reaction, the intermediate derivative (IV) was not obtained but hydrolyzed to free D-glucuronide III.
AN 1969:413291 HCAPLUS <<LOGINID::20080722>>
DN 71:13291
OREF 71:2451a,2454a
TI Metabolism of drugs. LX. Synthesis of codeine and morphine glucuronides
AU Yoshimura, Hidetoshi; Oguri, Kazuta; Tsukamoto, Hisao
CS Fac. Pharm. Sci., Kyushu Univ., Fukuoka, Japan
SO Chemical & Pharmaceutical Bulletin (1968), 16(11), 2114-19
CODEN: CPBTAL; ISSN: 0009-2363
DT Journal
LA English